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Modern Concepts of Cardiovascular Disease

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MYOCARDIAL INFARCTION AND ITS TREATMENT WITH ANTICOAGULANTS: A Summary of the Findings for 1031 Cases

The Committee on Anticoagulants of the American Heart Association was established in 1946 to determine the value of anticoagulants in the treatment of myocardial infarction. Teams headed by outstanding cardiologists supervised controlled series in 16 hospitals. Since the newer anticoagulants were not then available, dicumarol was the principal anticoagulant used, supplemented occasionally in the initial stages by heparin. Cases admitted on odd days were assigned to the group receiving anticoagulants (provided contraindications were not present) and cases admitted on even days, to the group receiving conventional therapy. Cases dying within 24 hours of hospitalization were omitted. Observations were continued consistently for a six-week period and reported in detail to the Central Laboratory. On this basis, in the course of two years, a pooled series of 1031 hospitalized cases of definitely diagnosed coronary thrombosis with myocardial infarction was accumulated.

A preliminary report, based on the first 800 cases, was published in 1948 (1). The full analysis of the total series, including a detailed study of the autopsy findings, is now nearing completion (2). This brief resume can include only a few of the major conclusions.

Clinical Findings

Thromboembolic complications—Twenty-six per cent of the 442 control cases in the final series developed thromboembolic complications during the six-week period of observation as contrasted with only 11 per cent of the 589 treated cases. Control group cases averaged 42 thromboembolic complications per hundred cases during the period studied and the treated group, only 13 complications per hundred cases, or less than a third as many. Both differences are highly significant statistically. The treated group had a substantially lower incidence than the control group of all types of thromboembolic complications, including venous thromboses and intracardiac complications (extensions and new secondary infarctions), but contrasts were particularly dramatic for cerebral, visceral, and peripheral emboli which, when combined, showed treated group rates less than a sixth of control levels. Study of complications during comparable periods of the illness indicated that the differences in complications were significant only during those portions of the total illness period when anticoagulants were in use.

Study of the prognosis for thromboembolic complications indicated that, while such complications were not individually predictable, they were in general higher among the following types of patients than among their opposites: (1) those who were severely ill at onset, (2) those who were 10 per cent or more overweight, (3) those in older age groups, (4) those who had already developed one or more thromboembolic complications, (5) those who developed congestive heart failure or shock after the initial period, and (6) those with auricular fibrillation or heart block. Such patients are, therefore, particularly in need of anticoagulant therapy. Significant variations in risk were not associated with sex or site of infarction. The percentage reduction proportionate to corresponding control group levels remained remarkably consistent for the numerous subgroups studied. Moreover, no subgroup of reasonable size could be identified that showed, in the absence of anticoagulant therapy, less than 28 thromboembolic complications per hundred cases. In view of the potentially serious consequences for the patient of thromboembolic phenomena (as, for example, hemiplegia or a gangrenous leg), this level is considered sufficiently high to warrant the use of anticoagulant therapy for all cases, including mild ones, where positive contraindications do not exist and adequately controlled anticoagulant therapy is feasible.

Deaths—Since deaths in myocardial infarction result from numerous conditions in addition to thromboembolic complications (congestive heart failure, shock, rupture, etc.), the substantial reductions in complications were only partially reflected in a reduced death rate. Among the 442 control group cases, 23.4 per cent died within six weeks, as contrasted with 16.0 per cent of the 589 treated group cases. Forty-two per cent of the con-

trol group deaths but only 23 per cent of the treated group deaths were preceded by a clinically diagnosed thromboembolic complication. During the period of potentially effective anticoagulant therapy, namely, the fourth day of therapy through four days after the last dose of dicumarol, only 9.5 per cent of the treated group cases died, or only slightly more than half the figure of 17.4 per cent for control group deaths during the corresponding period of their illness — a statistically significant difference. In contrast, differences during unprotected periods were minor and insignificant.

The risk of death was found particularly high for the following types of patients: (1) those age 60 and over, (2) those 10 per cent or more overweight, (3) those with a history of congestive heart failure, diabetes, arteriosclerosis, or hypertension, (4) those showing persistent congestive heart failure, or shock, or definite uremia, and (5) those who developed a thromboembolic complication during their illness. When patients were characterized by their status during the initial period or the first week, the following types showed a poor prognosis: (1) those evaluated initially as severely ill or as poor risk cases, (2) those showing certain abnormal rhythms, particularly auricular fibrillation and heart block, (3) those with leukocyte counts of 20,000 ccm. or more, (4) those with rectal temperatures of 103 deg. F or more, (5) those showing a drop of either 60 mm. systolic or 40 mm. diastolic or more below their usual blood pressure level, and (6) those with a maximum pulse of 120 or more. Many patients showed more than one of these unfavorable prognostic signs. After standardization for age, the following showed no conspicuous or statistically significant association with a high mortality: sex, site of infarction, a history of coronary artery disease or of anginal syndrome.

In comparison with the findings for thromboembolic complications reductions in deaths associated with anticoagulant therapy were less consistent percentagewise and less dramatic. With infrequent, minor and insignificant exceptions, however, when subclasses were compared they reflected some margin of savings. Reductions in deaths in the treated group were particularly dramatic for patients: (1) 10 per cent or more overweight, (2) with diabetes, (3) with auricular fibrillation in the first week, and (4) 60 years of age and over. Certain other types of patients severely threatened by their attack showed minimum improvement in deaths in spite of a substantially improved record for thromboembolic complications. For many of these, a fatal termination was doubtless inevitable regardless of anticoagulant therapy.

The findings do not support the policy recommended by some of treating only patients appearing severely ill at onset and of deferring anticoagulant treatment in milder cases until complications occur. When the findings for complications and deaths were considered jointly, they failed to identify any group that, in the absence of contraindications, should be excluded from anticoagulant therapy on the grounds that no potential benefits can be anticipated. Those mildly or moderately ill showed a death rate of 14 per cent in the control group as compared with 7 per cent in the treated group. When good risk cases, classified by multiple criteria, approximating those of Russek *et al.* (3), were separately considered, the percentage of good risk cases dying was below 2 per cent in both treatment groups. Nevertheless, thromboembolic complications in these same cases remained at the high level of 29 per hundred cases in the control group as contrasted with 9 per hundred in the treated group.

Confirmation of findings on complications and deaths — Not only were major differences in deaths and thromboembolic complications that were favorable to anticoagulants maintained consistently as the study progressed, but they also have been further confirmed by numerous other studies. For example, a further series of the American Heart Association which compared the effects of dicumarol and Tromexan (4) subsequently confirmed that additional myocardial infarction cases treated with anticoagulants showed a low risk of death and thromboembolism similar to that for the treated group in the earlier dicumarol series. Various independent studies using control groups furnish further confirmation: the series of Smith and his co-workers at Henry Ford Hospital, Detroit (5), Vander Veer, Marshall, and Kue at the Pennsylvania Hospital (6), Peters, Doenges, and Brambel at Mercy Hospital, Baltimore (7), Greisman and Marcus at Lincoln Hospital, New York (8), Schilling at St. Luke's Hospital, New York (9), Mullins and his co-workers at Mercy Hospital, Pittsburgh (10), Manchester in Washington, D.C. (11), Rashkoff and his co-workers at Mt. Sinai Hospital, New York (12), Tulloch and Gilchrist in Edinburgh (13), and most recently, Loudon, Pease and Cooke at the Radcliffe Infirmary, Oxford (14). Numerous other physicians, among them such pioneers as Nichols of Miami, have also contributed substantially through their early clinical trials of anticoagulant therapy in myocardial infarction. While there have been a few workers who have not confirmed these results, these exceptions may be attributed to the use of cases from back records not originally collected with special care with this problem in mind, to chance fluctuations in small samples, to the selection for treatment of the more severe cases, or to suboptimal therapy. When all available evidence is considered, the combined sequence of outcomes is highly significant statistically and cannot be reasonably attributed to chance.

Hemorrhages — Use of anticoagulants was associated with an increase in bleeding observed clinically. Five per cent of the control group and 13 per cent of the treated group showed some bleeding, mostly minor in nature, the principal types being hematuria, hematemesis, melena, hemoptysis, and epistaxis. Bleeding believed due to, or aggravated by, anticoagulants averaged 9 episodes per hundred cases in the treated group. Bleeding due to other causes was of equal frequency in the two groups. More than half of the related episodes were mild in nature, principally microscopic hematuria, and another two-fifths were moderate in severity. Only 4 episodes were severe. Bleeding was more frequent, regardless of treatment, in the presence of azotemia and renal and liver diseases, but even among these patients, more than two-thirds escaped without bleeding during therapy.

Other consequences of anticoagulant therapy — A careful study of numerous other characteristics of the course of the illness failed to identify any unfavorable consequences of anticoagulant therapy other than hemorrhage. In general, the course of the illness appeared favorably affected. The percentage of cases evaluated as severely ill at onset by their attending physician, that became mild or moderate in severity during the course (as judged by these same physicians) was considerably greater in the treated group than in the control group and contrariwise, the percentage of cases similarly judged mild or moderate at onset becoming severe during the course of the illness was nearly twice as great in the control as in the treated group. Various specific conditions were less frequent in the treated than in the control group during later weeks of the illness, notably, the development of new congestive heart failure and shock.

Findings pertinent to treatment procedures — An analysis of thromboembolic complications in relation to specific prothrombin times revealed that while some therapeutic effect was evident with minor prolongations, the lowest incidence of thromboembolic complications was not achieved until prothrombin times were prolonged to at least 25 to 39 seconds. Prolongation beyond this range yielded no additional advantage. Since the incidence of hemorrhage was found to increase rapidly as times were prolonged beyond 39 seconds, it was concluded that 25 to 39 seconds* (23 to 11 per cent prothrombin activity) was the optimum therapeutic range for anticoagulant therapy. In addition, the findings regarding early complications underscored the need for initial rapid achievement of this therapeutic range. Heparin and/or Tromexan have been helpful for this purpose. Since, in the absence of anticoagulant therapy, both thromboembolic complications and deaths were found to occur frequently through the fourth week of the illness, four weeks should be considered the minimum period of such therapy unless bleeding occurs. When thromboembolic complications have intervened, a longer period of therapy is indicated. The technics for administering dicumarol, Tromexan, and heparin and for the necessary laboratory tests are described in (15), pp. 54 ff.

Anticoagulants should be used cautiously or not at all in the following conditions: (1) prothrombin deficiency (hypoprothrombinemia), found with vitamin K deficiency or severe hepatic disease, (2) vitamin C deficiency, (3) renal insufficiency, (4) blood dyscrasias with impairment of normal mechanisms for hemostasis, (5) late pregnancy, (6) subacute bacterial endocarditis, (7) ulcerations and open wounds, (8) recent surgical operations on the brain or spinal cord, (9) operations performed in the presence of obstructive jaundice, external biliary fistula, or severe liver damage, (10) operations leaving raw surfaces, and (11) postoperative tube drainage of wounds or viscera.

When hemorrhage occurs during the administration of coumarin compounds in spite of these precautions, as will occasionally happen, it should be treated by withholding anticoagulants and giving 60-72 mg. water soluble vitamin K once or twice. If bleeding is severe, give 250-500 mg. vitamin K_1 oxide orally, followed, if necessary, by 300-500 cc of fresh whole blood or plasma. If hemorrhage occurs during the use of heparin as the sole anticoagulant, discontinue its use and if necessary give whole blood transfusions. Vitamin K preparations are not indicated unless the prothrombin time is prolonged. If cardiac tamponade appears to be developing under anticoagulant therapy, pericardial puncture and drainage should be used.

General characteristics of patients — Analysis of characteristics of the total sample revealed the following findings of interest (stated in approximate terms): (1) half had a history of coronary artery disease, (2) one-fourth had had a previous infarction, (3) 4 in 10 had a history of hypertension, (4) one-fourth had an elevated cholesterol level, and (5) 11 per cent had a history of diabetes (a very high proportion in comparison with the general population figure of about 1 to 5 per cent). The group as a whole was not characterized by overweight although the outcome was less favorable in overweight cases. Significant polycythemia was not found characteristic. The women were on the average about 6 years older than the men and even after correction for age, a substantially higher proportion of women had a history of diabetes (22 per cent *vs.* 7 per

* For clinical purposes two to two and one-half times the control prothrombin time is satisfactory if the control time is 12-18 seconds.

cent) and history of hypertension (64 per cent *vs.* 38 per cent).

Comparability of the treatment groups — Careful comparison of the control and treated groups with respect to numerous characteristics prior to the onset of the attack and during the early days thereafter showed the two groups to be remarkably similar. With very minor exceptions, differences noted were small, well-balanced in the direction of their probable influence on outcomes, and not statistically significant. Thus, while occasional exceptions to the strict application of the odd and even-day procedure for the selection of cases for treatment occurred, these do not appear to have been made in a manner that destroyed the comparability of the two groups as ultimately analyzed. For certain of the exceptions it was possible to make statistical corrections. The final report will support in detail the conclusion that the use of anticoagulant therapy offers the only plausible explanation available for the substantial and consistent pattern of outcomes favorable to the treated group.

Autopsy Findings

General findings — Ninety-one of the cases in this series were examined at autopsy. The diagnosis of acute myocardial infarction was found correct in 98 per cent of the cases, the two erroneous diagnoses being made in cases with evidences of old myocardial infarctions. Both the presence and the location were correctly diagnosed in 87 per cent of the autopsied cases. Nearly three-fourths of the original infarctions were found due to thrombotic occlusions. Only 3 per cent were due to subintimal hemorrhage, the rest being due to coronary insufficiency without occlusion or to miscellaneous causes. Severe arteriosclerosis was evident in the coronary arteries in 88 per cent of the cases examined at autopsy; in the aorta, in 54 per cent; in the cerebral vessels, in 24 per cent; in the renal arteries, in 12 per cent; and in the pulmonary arteries, in 7 per cent of the cases with corresponding organs examined.

Thromboembolic complications — Even though many of the autopsy cases died early, frequently preventing the treated cases from receiving a significant period of adequate anticoagulant therapy, two-thirds of the untreated cases but only a third of the treated autopsy cases showed mural thrombi at autopsy. Treated cases that did show mural thrombi had fewer chambers of the heart involved than did untreated cases. Extracardiac thromboembolic complications (emboli, infarctions, or thrombi) average 125 per hundred among untreated cases but only 45 per hundred among treated cases. These involved, in descending order of frequency, the lungs, kidneys, aorta, brain, spleen, liver and adrenal glands. Only 13 per cent of these extracardiac complications had been diagnosed clinically. Undiagnosed thromboembolic phenomena were much more frequently found at autopsy in untreated than in treated cases, a fact that implies that the clinical findings on complications understate the degree of contrast that prevailed.

Hemorrhages and ruptures — Fifty-two per cent of the untreated cases as compared with 66 per cent of the treated cases showed some degree or type of intracardiac hemorrhage other than rupture on gross examination and an additional 11 and 20 per cent respectively showed microscopic hemorrhage. While this contrast is based on a small sample and tends also to be exaggerated by the fact that the number of treated cases coming to autopsy with thromboembolic phenomena is reduced as a direct result of anticoagulant therapy, some of this difference in prevalence of hemorrhage is undoubtedly due to anticoagulant therapy. Since counts include very minor hemorrhages, not all the difference reflects bleeding of significance to the patient. The high rate among untreated cases indicates, moreover, that bleeding is a common characteristic of myocardial infarction as of infarction in other sites. Cardiac ruptures number 4 among the 48 untreated autopsy cases and 8 among the 41 treated autopsy cases with myocardial infarction. No increase in subintimal hemorrhage of the coronary arteries was found associated with therapy.

Extracardiac hemorrhage was relatively uncommon in both groups. Seventeen per cent of the untreated group as compared with 20 per cent of the treated group showed some extracardiac hemorrhage on gross autopsy examination. These involved 2.0 and 2.7 per cent respectively of the organs examined. None outside the heart contributed to death.

An evaluation of the role of hemorrhage and rupture in the deaths of the patients, plus the use of the assumption that the causes of death in nonautopsy fatal cases were proportionately similar, led to the estimate that 2.4 per cent of all untreated cases and 4.1 per cent of all treated cases died with rupture or hemorrhage (mostly hemopericardium) as an immediate or contributing cause of death. It was therefore estimated that if this difference is typical and not due to chance, the risk that anticoagulants will contribute to the death of the patient, given comparable cases and treatment procedures, is perhaps on the average about 1.7 cases per hundred treated with anticoagulants. This estimate includes all ruptures or hemorrhages identifiable either clinically or at autopsy. In this study, this risk was compensated for many fold by the reduction in deaths with thromboembolism, as the substantially lower total *net* death rate for treated cases makes evident.

While some contend that this degree of risk is unjustified for patients only mildly ill (good risk cases) whose total death rate may not exceed 2 per cent, this argument fails to take into account the probability that the risk of death from rupture or hemopericardium is undoubtedly also correlated with the severity of the case and the general risk of death for the size of the original infarction, the presence of hypertension and pericarditis, and the general condition of the heart all clearly increase the risk of both rupture and hemopericardium, the two major risks involved. If this is true, the risk that hemorrhage or rupture would contribute to the death of a *good risk case* would thus be considerably below this general estimated 1.7 per cent level. Evidence from the present series supports this position. Among all the 16 cases in the present series in which hemorrhage or cardiac rupture was an immediate or contributing cause of death in either treatment group, all except one were poor risk cases according to Russek's criteria (3). With improved procedures for classification, this single case (an 84-year-old female with cardiac rupture) would also have been considered a poor risk case since this patient obviously had a large infarction, was hypertensive and was classified as severely ill at onset by the attending physician. The patient did not happen, however, to show any of Russek's signs for discriminating poor risk cases.

From the experience in this series, therefore, it seems highly improbable that the *net* risk of death (i.e., savings balanced against losses) would be increased on the average by the use of anticoagulant therapy in good risk cases *provided* that the patients were well screened for contraindications and that such therapy was properly controlled. In view of the protection afforded against disabling and possibly fatal thromboembolic complications, the minimal hemorrhagic risk involved for these good risk patients in anticoagulant therapy seems justified.

Conclusions

Valid statistical evidence compiled from carefully controlled and studied hospital case material indicates that anticoagulants correctly used exert a markedly favorable influence on both the death rate and the thromboembolic complication rate associated with myocardial infarction for cases that survive the initial impact of the attack. When anticoagulants are correctly used, the risk of hemorrhage is not excessive and is reduced as the physician gains experience. The therapy is not, however, one for the careless physician or for one who does not fully understand the objective, methods and contraindications of the technic. That this technic can be mastered and used successfully has been amply demonstrated by the experience of hundreds of physicians in many areas both in the United States and abroad. Since there is real risk to the patient in waiting for the course to worsen or the first thromboembolic complication to develop before using anticoagulants, this therapy should not be reserved for patients severely ill at onset.

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The opinions and conclusions expressed herein are those of the authors and do not necessarily represent the official views of the Scientific Council of the American Heart Association.

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ANNUAL MEETING OF THE AHA, 1954

The Annual Meeting of the American Heart Association in 1954 will be held at the Conrad Hilton Hotel in **Chicago.** The Assembly Panels and the General Assembly will be held on Thursday and Friday, April 1 and 2, and will be followed by a specific scientific program on clinical cardiology on Saturday and Sunday, April 3 and 4, conducted under the auspices of the newly formed Section on Clinical Cardiology of the Scientific Council. These sessions will immediately precede the annual meeting of the American College of Physicians.

SCIENTIFIC PROGRAM OF THE SECTION ON CLINICAL CARDIOLOGY, 1954

The Section on Clinical Cardiology of the American Heart Association will sponsor a two-day scientific program at the Conrad Hilton Hotel in Chicago on April 3 and 4, 1954. This program will constitute a portion of the Annual Meeting of the American Heart Association and immediately precedes the Annual Sessions of the American College of Physicians. The meeting will be open to all members of the medical profession. Doctor Wright R. Adams of Chicago is Chairman of the Program Committee. Members of the American Heart Association who wish to present papers should send a 250-300 word abstract of the proposed paper to Doctor Charles D. Marple, Medical Director, American Heart Association, Inc., 44 East 23rd Street, New York 10, New York. *All papers should be on subjects of distinct clinical interest. The deadline for the receipt of abstracts is January 1, 1954.*

ANNUAL SCIENTIFIC SESSIONS, 1954, and THE SECOND WORLD CONGRESS OF CARDIOLOGY

The Second World Congress of Cardiology and the 27th Scientific Sessions of the American Heart Association will be held jointly in Washington, D. C., September 12-17, 1954. Membership in the Congress will be open to all members of the American Heart Association; nonmembers may attend by special invitation of the Organization Committee.

American and Canadian scientists desiring to present papers should submit titles with abstracts of not over 200 words, typewritten, double-spaced, in duplicate. They should be addressed to Charles D. Marple, M.D., Medical Director, American Heart Association, 44 East 23rd Street, New York 10, N. Y., and *must be received on or before April 1, 1954.*

The Formal Announcement of the combined meeting will be distributed widely to the medical profession within the month. For further information, address Dr. L. W. Gorham, Secretary-General, Second World Congress of Cardiology, 44 East 23rd Street, New York 10, N. Y.